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14. ABSTRACT

The purpose of the research effort is to test two advanced MRI methods, DTI and resting-state fMRI, in active-duty military blast-related TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. These methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics. The overarching hypothesis guiding this project is that traumatic axonal injury is a principal cause of impaired brain function following blast-related TBI. The major findings as of 1 Aug 2009 are as follows:

1) All required human studies/IRB/HRPO approvals have been obtained.
2) A total of 63 subjects have been enrolled at Landstuhl Regional Medical Center, including 43 blast-related TBI patients and 20 controls. All acute MRI scans have been performed successfully with no adverse events.
3) Initial analyses of initial scans have revealed abnormalities on DTI indicative of traumatic axonal injury in 20/43 injured subjects that were not detectible on conventional MRI or CT.
4) To date, 4 clinical outcome evaluations and repeat scans have been performed at Washington University with no adverse events.

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Table of Contents

Page

Introduction:
The purpose of the research effort is to test two advanced MRI methods- DTI and resting-state fMRI- in active-duty military blast-related TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. These methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics. The overarching hypothesis guiding this project is that traumatic axonal injury is a principal cause of impaired brain function following blast-related TBI.

Body:
The research accomplishments associated with the tasks outlined in the Statement of Work as follows.

Task 1) to obtain DTI, resting-state fMRI and conventional MRI scans acutely after injury at Landstuhl Regional Medical Center (LRMC) on a total of 100 military personnel, 80 who have sustained blast-related TBI and 20 who have sustained other injuries, but have no evidence of TBI.

All required human studies/IRB/HRPO approvals have been obtained from Washington University and Brooke Army Medical Center, which oversees LRMC. All the logistics involved in enrolling subjects and performing scans at LRMC have been addressed. A total of 99 active duty US military personnel were screened at LRMC from 13 Nov 2008 - 26 Dec 2008 and 2 Feb 2009 - 24 Feb 2009 (See **Table**). A total of 63 subjects provided written informed consent and were enrolled in the study; 43 had sustained acute blast-related TBI and 20 had sustained other blast-related injuries but have no evidence of TBI. High quality DTI, resting-state fMRI and conventional MRI scans have been acquired in all 63. All participants have been screened carefully for contraindications to MRI. There have been no adverse events resulting from the scans.

Table

Subjects screened:	99		
	Enrolled:	63	
	Excluded due to TBI caused by non-blast-related mechanism:	4	
	Eligible but did not consent:	5	
	Excluded due to prior significant TBI:	1	
	Excluded due to brain tumor:	1	
	Excluded due to contraindications to MRI:	17	
		Metallic shrapnel:	8
		Other metal:	2
		Claustrophobia:	2
		Clinically unstable:	5
	Not enrolled to prevent interference with clinical care:	3	
	Not enrolled to protect patient confidentiality (Special Forces):	5	

The MRI scanner at LRMC has been undergoing and upgrade and there has been a large backlog of clinical cases, so it was not been possible to enroll further participants between 24 Feb 2009 and the present time. These

issues should be resolved within the next 1-2 months and we intend to enroll an additional 37 subjects with blast-related TBI.

Task 2) to collect detailed clinical information on TBI-related outcomes 6-12 months after injury on the same participants recruited for Task 1. This will include global outcome assessments, neuropsychological testing for memory, attention and executive function deficits, motor performance measures, and clinician administered rating scales for depression and post-traumatic stress disorder. Repeat DTI, resting-state fMRI and conventional MRI will be performed to track the evolution of the injuries.

We have completed 4 of these evaluations and have established all of the logistics required to bring injured service members to St. Louis for 1-2 days. These include systematic monthly phone or email contact with the participants and their family members to maintain updated contact information, request for permission to travel procedures for active-duty service members in the US, and efficient coordination of all assessments. There have been no complications or adverse events to date in this phase. We have engaged a clinical coordinator, Ms. Anne Johnson, at Washington University to assist with these logistics. We have hired and trained 5 psychometricians to perform neuropsychological testing and conduct structured interviews.

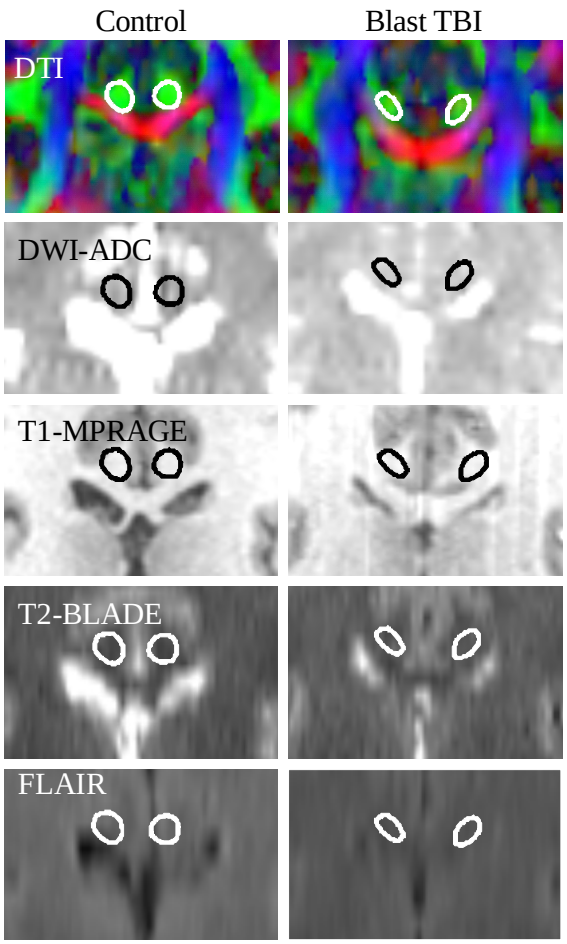

Figure: Acute blast-related TBI patient with apparent traumatic axonal injury in the cingulum bundles bilaterally (outlined). DTI signal abnormality is indicated by less intense green signal in comparison to a control subject. No abnormalities were seen on conventional MRI (DWI-ADC, T1-MPRAGE, T2-BLADE, FLAIR) in this region.

Task 3) to extensively analyze the acute imaging predictors and correlates of 6-12 month clinical outcomes. Several prespecified hypotheses based on known brain anatomical-clinical correlations will be tested. Also, exploratory approaches will be used as the structural bases for many post-traumatic deficits and disorders are not well understood.

All DTI and conventional MRI scans acquired to date have been analyzed using quantitative multi-slice region-of-interest methods. Regions of interest have included the following white matter tracts:

1) Genu of the corpus callosum
2) Body of the corpus callosum
3) Splenium of the corpus callosum
4) Left anterior limb or the internal capsule
5) Right anterior limb or the internal capsule
6) Left posterior limb or the internal capsule
7) Right posterior limb or the internal capsule
8) Left cingulum bundle
9) Right cingulum bundle
10) Left uncinate fasciculus
11) Right uncinate fasciculus

Quantitative signal abnormalities have been found in 20 of 43 blast-related TBI patients using DTI, none of which were apparent on conventional MRI (see **Figure**). The clinical significance of these abnormalities has not yet been determined.

Key Research Accomplishments:

- All required human studies/IRB/HRPO approvals have been obtained.
- A total of 63 subjects have been enrolled at Landstuhl Regional Medical Center, including 43 blast-related TBI patients and 20 controls. All acute MRI scans have been performed successfully with no adverse events.
- Initial analyses of initial scans have revealed abnormalities on DTI indicative of traumatic axonal injury in 20/43 injured subjects that were not detectible on conventional MRI or CT.
- To date, 4 clinical outcome evaluations and repeat scans have been performed at Washington University with no adverse events.

Reportable Outcomes:

Abstracts:

1) Brody, DL et al "Advanced Magnetic Resonance Imaging in Blast-related Traumatic Brain Injury"
To be presented at the Military Health Research Forum (MHRF), September 2009

2) Mac Donald, CL et al "Advanced MR Imaging of Active Duty Military Personnel following Acute Blast-Related Traumatic Brain Injury"
To be presented at the National Neurotrauma Society meeting, September 2009

Conclusion: An advanced MRI study of acute blast-related TBI in US military personnel is feasible. These advanced MRI methods have demonstrated abnormalities indicative of traumatic axonal injury that were not detected using standard MRI or CT. This approach, if successful, has the potential to dramatically advance the acute assessment of patients with blast-related TBI, and may generalize to other injury mechanisms as well. In a military setting, it may allow improved triage / return-to-duty decisions to be made, and provide early guidance with regard to appropriate rehabilitative strategies.

References:

None.

Appendices:

None.